PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 11 August 2000 (11.08.00)	
International application No. PCT/US99/30004	**Applicant's or agent's file reference** SF0977X
International filing date (day/month/year) 29 December 1999 (29.12.99)	**Priority date** (day/month/year) 31 December 1998 (31.12.98)
Applicant BATES, Elizabeth et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

20 June 2000 (20.06.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
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1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Charlotte ENGER

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PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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To:

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NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

	Date of mailing *(day/month/year)* 30.03.2001
Applicant's or agent's file reference SF0977X – WI	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/30004	29/12/1999	31/12/1998

Applicant
SCHERING CORPORATION et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Büchler, S Tel.+49 89 2399-8090

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
SF0977X		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/30004	29/12/1999	31/12/1998
International Patent Classification (IPC) or national classification and IPC		
C12N15/12		
Applicant		
SCHERING CORPORATION et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20/06/2000	30.03.2001
Name and mailing address of the international preliminary examining authority:	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Wimmer, G Telephone No. +49 89 2399 7347

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/30004

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-25 as originally filed

Claims, No.:

1-16 as originally filed

Sequence listing part of the description, pages:

1-14, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:
   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-16 (all partially).

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2, 4, 5
	No:	Claims	1, 3, 6-16
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-16
Industrial applicability (IA)	Yes:	Claims	1-16

No: Claims

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item IV

Lack of unity of invention.

The application lacks unity as required by Art. 3(4)(iii) PCT and Rule 13 PCT.

Reference is made to the following document:

D1: WO 98 24906 A (SCHERING CORP) 11 June 1998 (1998-06-11) cited in the application

Rule 13.1 PCT states that for unity of invention to be present, all subject-matter should be linked by a single general inventive concept.

Various sequences for genes and proteins derived from activated monocytes have been provided and claimed in the present application. Specifically, the gene and protein sequences describe the human FDF03 gene and protein, and four FDF03 homologs.

The technical feature common to these genes and proteins is that they represent variants of human FDF03.

As the applicants themselves elaborate in the description, the human FDF03 gene and protein have been isolated and described previously (D1). Therefore, the technical feature common to the genes and proteins provided by the current application lacks novelty, and a "single general inventive concept" as required by Rule 13.1 PCT is lacking.

The genes and proteins described in this application must therefore be regarded as representing 5 possible solutions to this problem, thus 5 different inventions, and are grouped as follows:

Group	protein	SEQ IDs
I	FDF03	1, 2
II	FDF03-[SPEC0808]TM	3, 4
III	FDF03-S1	5, 6
IV	FDF03-M14	7, 8
V	FDF03-S2	9, 10

In their reply of 4.12.2000 to the Invitation to Restrict or to Pay Additional Fees, the applicants requested that examination be carried out for the second group, i.e. the FDF03-[SPEC0808]TM gene and protein.

Accordingly, all claims were subject to the examination, and references to sequences SEQ IDs 1-2 and 5-10 were disregarded.

Re Item V

Reasoned statement under Art. 35(2) PCT with regard to novelty, inventive step or industrial applicability.

The application does not meet the requirements of Art. 33 PCT since claims 1, 3, and 6-16 are not novel, and claims 1-16 do not appear to contain an inventive step.

Novelty under Art. 33(2) PCT.

1) The term "derived from" in claims 1, 3, 15 and 16 is vague and open to interpretation. In particular, also the wild-type human FDF03 gene and protein, which were already disclosed in document D1 (SEQ IDs 1 and 2), can be viewed as being "derived from" sequence SEQ ID 3 or 4, respectively. Since no limits as to the maximal degree of variation are given, these claims must be viewed as not being novel.

   Through their dependence on one of these claims, also claims 6, 10, 11 and 12 are not novel.

2) However, it appears that the prior art does not contain an FDF03 variant with according modifications.
   While claim 2 is not ultimately clear (see sect. VIII.2), the IPEA assumed that this claim is directed to a polypeptide comprising an amino acid sequence of SEQ ID No. 4. In this case, the claim is novel.
   The same applies to claim 4.

3) No nucleic acid sequence as laid out in SEQ ID 3 was disclosed in the prior art. Consequently, claim 5 is novel.

4) It is not possible to examine which substances are embraced by the terms of claim 7. However, also antibodies against wild-type FDF03 will fall within this claim, making the claim not novel.
The same applies to claims 8 and 9.

5) It must appear obvious to the skilled person that nucleotide sequences of only 8 consecutive nucleotides, moreover out of > 900 possible combinations, will frequently appear in many other, unrelated sequences. Claims 13 and 14 can therefore not be considered to be novel.

Inventive Step under Art. 33(3) PCT.

6) The technical problem solved by the present invention was the provision of alternatives to the FDF03 gene and protein.
However, the solution, the provision of a splice variant thereof, cannot be viewed as being inventive.
To solve the technical problem, the skilled person would use standard techniques based on the known FDF03 gene, such as PCR amplification with degenerate primers from a cDNA bank, or low stringency hybridization, to screen for related genes. Therein, the skilled person would have a high chance of success to arrive at such an FDF03 variant.
No inventive step is therefore acknowledged for the provision of the nucleotide and amino acid sequences SEQ IDs 3 and 4. Consequently, all of claims 1-16 fail to comply with Art. 33(3) PCT.

Re Item VIII

Certain observations and clarity.

1) The term "derived from" in claims 1 and 15 is vague and open to interpretation, since no limits as to the maximal degree of variation are given.

2) The term "the mature protein" in claims 2 and 4 is not ultimately clear. The IPEA assumes that a protein with amino acid sequence of SEQ ID No. 4 was intended.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: MONOCYTE–DERIVED NUCLEIC ACIDS AND RELATED COMPOSITIONS AND METHODS

(57) Abstract

Nucleic acids encoding various monocyte–derived proteins and related compositions, including purified proteins and specific antibodies are described. Methods of using such composition are also provided.

FOR THE PURPOSES OF INFORMATION ONLY

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MONOCYTE-DERIVED NUCLEIC ACIDS AND RELATED COMPOSITIONS AND METHODS

Field Of The Invention

The present invention is directed to compositions related to genes found in monocytes, cells which function in the immune system. These genes function in controlling development, differentiation, and/or physiology of the mammalian immune system. In particular, the invention provides nucleic acids, proteins, antibodies, and methods of using them.

Background Of The Invention

Monocytes are phagocytic cells that belong to the mononuclear phagocyte system and reside in the circulation. These cells originate in the bone marrow and remain only a short time in the marrow compartment once they differentiate. They then enter the circulation and can remain there for a relatively long period of time, e.g., a few days. Monocytes can enter the tissues and body cavities by a process known as diapedesis, where they differentiate into macrophages and possibly into dendritic cells. In an inflammatory response, the number of monocytes in the circulation may double, and many of the increased number of monocytes diapedese to the site of inflammation. For a review of monocytes and their functions, see, e.g., Gallin, *et al.* (eds), 1988, *Inflammation: Basic Principles and Clinical Correlates*, Raven Press, NY; van Furth (ed), 1985, *Mononuclear Phagocytes: Characteristics, Physiology and Function*, Martinus Nijhoff, Dordrecht, Netherlands.

Antigen presentation refers to the cellular events in which a proteinaceous antigen is taken up, processed by antigen presenting cells (APC), and then recognized to initiate an immune response. The most active antigen presenting cells have been characterized as the macrophages, which are direct developmental products from monocytes; dendritic cells; and certain B cells.

Macrophages are found in most tissues and are highly active in internalization of a wide variety of protein antigens and microorganisms. They have a highly developed endocytic activity, and secrete many products important in the initiation of an immune response. For this reason, it is believed that many genes expressed by monocytes or induced by monocyte activation are important in antigen uptake, processing, presentation, or regulation of the resulting immune response.

Despite the importance of monocytes to immune system function, these cells remain poorly characterized, both in terms of the proteins they express and in terms of many of their functions, in particular, the processes and mechanisms related to the initiation of an immune response, including antigen processing and presentation. There is thus a need in the art for agents useful in the diagnosis and treatment of medical conditions caused by, e.g., the inappropriate regulation, development, or physiology of antigen presenting cells.

Summary Of The Invention

The present invention fulfills this need by providing compositions and methods for determining the presence, amount, distribution and normalcy of certain gene products and for facilitating the discovery of agents for treating certain disease states.

The invention is based upon the discovery of novel genes and gene products isolated from activated monocytes.

The invention provides isolated nucleic acid sequences comprising at least about 12, preferably at least about 18, most preferably at least about 20-35, and most preferably 35-55 or more consecutive nucleotides shown in SEQ ID NO: 1, 3, 5, 7, or 9, or which encode an amino acid sequence shown in SEQ ID NO: 2, 4, 6, 8 or 10, including complete protein coding sequences, and complements thereof. The invention encompasses sequence-conservative variants and function-conservative variants of these sequences. The nucleic acids may be DNA, RNA, DNA/RNA duplexes, protein-nucleic acid (PNA), or derivatives thereof. The invention also encompasses recombinant DNA vectors (including DNA expression vectors) comprising these sequences; cells comprising such vectors, including bacterial, fungal, plant, insect, and mammalian cells; and methods for producing expression products comprising RNA and polypeptides encoded by the sequences.

Polypeptide sequences of the invention comprise at least eight, preferably at least about 10, and more preferably at least about 12 or more consecutive amino acid residues derived from SEQ ID NO: 2, 4, 6, 8 or 10. Function-conservative variants and homologs are included in the scope of the invention.

The invention further provides binding compositions, in particular antibodies, most particularly monoclonal antibodies, which specifically bind to polypeptides having an amino acid sequence shown in SEQ ID NO: 2, 4, 6, 8 or 10 or function conserved variants or homologs thereof. Methods are also provided for producing antibodies having the desired binding specificity in a host animal.

Detailed Description Of The Invention

All patent applications, patents, and literature references cited in this specification are hereby incorporated herein by reference in their entirety.

In practicing the present invention, many conventional techniques in molecular biology, microbiology, and recombinant DNA, are used. Such techniques are well known and are explained fully in, for example, Sambrook *et al.*, 1989, *Molecular Cloning: A Laboratory Manual*, Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York; *DNA Cloning: A Practical Approach*, Volumes I and II, 1985 (D.N. Glover ed.); *Oligonucleotide Synthesis*, 1984, (M.L. Gait ed.); *Nucleic Acid Hybridization*, 1985, (Hames and Higgins); *Transcription and Translation*, 1984 (Hames and Higgins eds.); Animal Cell Culture, 1986 (R.I. Freshney ed.); *Immobilized Cells and Enzymes*, 1986 (IRL Press); Perbal, 1984, *A Practical Guide to Molecular Cloning*; the series, *Methods in Enzymology* (Academic Press, Inc.); *Gene Transfer Vectors for Mammalian Cells*, 1987 (J. H. Miller and M. P. Calos eds., Cold Spring Harbor Laboratory); and *Methods in Enzymology* Vol. 154 and Vol. 155 (Wu and Grossman, and Wu, eds., respectively).

Definitions

1. A "monocyte-derived" nucleic acid or polypeptide refers to the source from which the sequence was originally isolated.

2. "Nucleic acid" or "polynucleotide" refers to purine- and pyrimidine-containing polymers of any length, either polyribonucleotides or polydeoxyribonucleotides or mixed polyribo-polydeoxyribo nucleotides. This includes single- and double-stranded molecules, i.e., DNA-DNA, DNA-RNA and RNA-RNA hybrids, as well as "protein nucleic acids" (PNA) formed by conjugating bases to an amino acid backbone. This also includes nucleic acids containing modified bases.

3. A "coding sequence" or a "protein-coding sequence" is a polynucleotide sequence capable of being transcribed into mRNA and/or capable of being translated into a polypeptide. The boundaries of the coding sequence are typically determined by a translation start codon at the 5'-terminus and a translation stop codon at the 3'-terminus.

4. A "complement" of a nucleic acid sequence refers to the "antisense" sequence that participates in Watson-Crick base-pairing with the original sequence.

5. An "isolated" nucleic acid or polypeptide refers to component that is removed from its original environment (for example, its natural environment if it is

naturally occurring). An isolated nucleic acid or polypeptide preferably contains less than about 50%, more preferably less than about 75%, and most preferably less than about 90%, of the cellular components with which it was originally associated.

6. A nucleic acid or polypeptide sequence that is "derived from" a designated sequence refers to a sequence that corresponds to a region of the designated sequence. For nucleic acid sequences, this encompasses sequences that are homologous or complementary to the sequence, as well as "sequence-conservative variants" and "function-conservative variants." For polypeptide sequences, this encompasses "function-conservative variants." Sequence-conservative variants are those in which a change of one or more nucleotides in a given codon position results in no alteration in the amino acid encoded at that position. Function-conservative variants are those in which a given amino acid residue in a polypeptide has been changed without substantially altering the overall conformation and function of the native polypeptide, including, but not limited to, replacement of an amino acid with one having similar physico-chemical properties (such as, for example, acidic, basic, hydrophobic, and the like). "Function-conservative" variants also include any polypeptides that have the ability to elicit antibodies specific to a designated polypeptide.

7. A "probe" refers to a nucleic acid or oligonucleotide that forms a hybrid structure with a sequence in a target region due to complementarity of at least one sequence in the probe with a sequence in the target.

8. Nucleic acids are "hybridizable" to each other when at least one strand of nucleic acid can anneal to another nucleic acid strand under defined stringency conditions. Stringency of hybridization is determined, e.g., by a) the temperature at which hybridization and/or washing is performed, and b) the ionic strength and polarity (e.g., formamide) of the hybridization and washing solutions, as well as other parameters. Hybridization requires that the two nucleic acids contain substantially complementary sequences; depending on the stringency of hybridization, however, mismatches may be tolerated. The appropriate stringency for hybridizing nucleic acids depends on the length of the nucleic acids and the degree of complementarity, variables well known in the art.

9. An "immunogenic component" is a moiety that is capable of eliciting a humoral and/or cellular immune response in a host animal.

10. An "antigenic component" is a moiety that binds to its specific antibody with sufficiently high affinity to form a detectable antigen-antibody complex.

11. A "sample" refers to a biological sample, such as, for example, tissue or fluid isolated from an individual or from an *in vitro* cell culture constituents, as well as samples obtained from laboratory procedures.

The invention provides nucleic acid sequences encoding mammalian proteins expressed on monocytes. While specific human monocyte-derived genes and gene products are described herein, the invention encompasses structurally (e.g., sequence) related embodiments from other sources or mammalian species, including polymorphic or individual variants. These will include, e.g., proteins which exhibit relatively few changes in sequence, e.g., less than about 5%, and number, e.g., less than 20 residue substitutions, typically less than 15, preferably less than 10, and more preferably less than 5 substitutions. These will also include versions which are truncated from full length and fusion proteins containing substantial segments of these sequences.

A gene/gene product, isolated from human monocyte cell library and designated FDF03, has been previously described in published International application WO 98/24906, the disclosure of which is incorporated herein in its entirety by reference. The FDF03 gene encodes a type I transmembrane protein comprising an extracellular portion characterized by Ig-like domains, indicating that this gene encodes a receptor member of the Ig superfamily.

SEQ NO: 1 shows the nucleic acid sequence encoding human FDF03 protein. The amino acid sequence of the FDF03 protein is shown in SEQ ID NO: 2. The putative coding region runs from about nucleotide 154 to nucleotide 1062. An N-terminal hydrophobic sequence corresponding to a putaive signal sequence runs from about amino acid residue -19 (Met) to amino acid residue -1 (Leu). An internal hydrophobic sequence corresponding to a putative transmembrane segment runs from about residue 177 (Ala) to residue 199 (Leu). The extracellular region is about 170 amino acids, with a potential Ig-like domain structure. The intracellular region is about 80 residues. Sequence analysis indicates similarity to GenBank clones H26010 and R50327 from humans.

Four human FDF03 homologs have now been discovered.

FDF03-ΔTM

The second human clone, designated FDF03-deltaTM (FDF03-ΔTM), appears to be a soluble form of human FDF03 generated by alternative splicing. The nucleic acid sequence encoding FDF03-ΔTM is shown in SEQ NO: 3. The amino acid sequence of the FDF03-ΔTM protein is shown in SEQ ID NO: 4.

cDNA of the FDF03-ΔTM molecule was amplified along with that of FDF03 during the analysis of human FDF03 expression by RT-PCR. Using primers designed in the 5'-UTR and 3'-UTR of FDF03 gene (FDF03-U25: 5'-ACAGCCCTCTTC-GGAGCCTCA (SEQ ID NO: 11) and FDF03-L1166: 5'-AAGCTGGCCCTGAACT CCTGG (SEQ ID NO: 12)), an approximately 200 base pair shorter band was amplified by RT-PCR from PMA/ionomycin activated PBL cDNA, then gel purified, cloned and sequenced. Different clones contained an identical insert of 943 base pairs with an open reading frame encoding a type I protein of 230 amino acids. The deduced amino acid sequence of FDF03-ΔTM matched perfectly with that of FDF03, but contained a gap of 73 amino acids that deleted the extracellular threonine-rich region and the transmembrane domain of FDF03. This resulted in a protein with a potential hydrophobic signal peptide followed by the extracellular Ig like-domain linked to the intracytoplasmic domain of FDF03. cDNA alignments with FDF03 sequence identified a deletion of 219 nucleotides in the FDF03-ΔTM sequence (FDF03 nucleotide 608 to 827) that did not introduce premature stop codons, suggesting that this molecule is the product of an alternative splicing. This molecule is believed to be a secreted soluble form of FDF03 and believed to bind to the same ligand(s) as FDF03.

The protein alignment of the FDF03 (SEQ ID NO: 2) and FDF03-ΔTM (SEQ ID NO: 4) is shown below.

```
1   MGRPLLLPLLPLLLPPAFLQPSGSTGSGPSYLYGVTQPKHLSASMGGSVEIPFSFYYPWE   FDF03
1   MGRPLLLPLLPLLLPPAFLQPSGSTGSGPSYLYGVTQPKHLSASMGGSVEIPFSFYYPWE   FDF03-ΔTM

61  LATAPDVRISWRRGHFHGQSFYSTRPPSIHKDYVNRLFLNWTEGQKSGFLRISNLQKQDQ   FDF03
61  LATAPDVRISWRRGHFHGQSFYSTRPPSIHKDYVNRLFLNWTEGQKSGFLRISNLQKQDQ   FDF03-ΔTM

121 SVYFCRVELDTRSSGRQQWQSIEGTKLSITQAVTTTTQRPSSMTTTWRLSSTTTTTGLRV   FDF03
121 SVYFCRVELDTRSSGRQQWQSIEGTKLSITQ----------------------------   FDF03-ΔTM

181 TQGKRRSDSWHISLETAVGVAVAVTVLGIMILGLICLLRWRRRKGQQRTKATTPAREPFQ   FDF03
152 ----------------------------------------GQQRTKATTPAREPFQ   FDF03-ΔTM

241 NTEEPYENIRNEGQNTDPKLNPKDDGIVYASLALSSSTSPRAPPSHRPLKSPQNETLYSV   FDF03
168 NTEEPYENIRNEGQNTDPKLNPKDDGIVYASLALSSSTSPRAPPSHRPLKSPQNETLYSV   FDF03-ΔTM

303 LKA                                                             FDF03
230 LKA                                                             FDF03-ΔTM
```

(- : deletion)

FDF03-S1

The third clone, designated FDF03-Short1 (FDF03-S1), is an Ig-like molecule homologous to FDF03 but with a short intracytoplasmic domain and a charged residue in

transmembrane domain. Comparative DNA and protein analysis suggests the presence of different genes for FDF03 and FDF03S1, rather than alternatively spliced products. The nucleic acid sequence encoding FDF03-S1 is shown in SEQ NO: 5. The amino acid sequence of the FDF03-S1 protein is shown in SEQ ID NO: 6.

FDF03-S1 is a type I transmembrane protein belonging to the Ig superfamily. FDF03-S1 contains a hydrophobic leader sequence followed by an extracellular region (~170 residues) with a V-type Ig domain structure homologous to that of FDF03 (88% homology at the amino acid level). Unlike FDF03, FDF03-S1 possesses a transmembrane domain with a charged amino acid (K), and a small intracellular tail (15 residues) without ITIM or internalization motif. FDF03-S1 is believed to represent an activation isoform of FDF03 and may associate with ITIM-bearing molecules such as DAP12. The amino acid sequence is shown below, wherein the signal peptide and transmembrane domain are underlined. The charged amino acid, lysine (K), residue (arrow) in the transmembrane domain may permit association with another chain, for example DAP12.

MGRPLLLPLLLLLQPPAFLQPGGSTGSGPSYLYGVTQPKHLSASMGGSVEIPFSFYYPWEL
AIVPNVRISWRRGHFHGQSFYSTRPPSIHKDYVNRLFLNWTEGQESGFLRISNLRKEDQSV
YFCRVELDTRRSGRQQLQSIKGTKLTITQAVTTTTTWRPSSTTTIAGLRVTESKGHSESWH
LSLDTAIRVALAVAVLKTVILGLLCLLLLWWRRRKGSRAPSSDF(SEQ ID NO: 6)
↑

The protein alignment of FDF03 (SEQ ID NO: 2) and FDF03-S1 (SEQ ID NO: 6) is shown below.

```
1    MGRPLLLPLLPLLLPPAFLQPSGSTGSGPSYLYGVTQPKHLSASMGGSVEIPFSFYYPWE  FDF03
1    MGRPLLLPLLLLLQPPAFLQPGGSTGSGPSYLYGVTQPKHLSASMGGSVEIPFSFYYPWE  FDF03-S1
               +  +        +

61   LATAPDVRISWRRGHFHGQSFYSTRPPSIHKDYVNRLFLNWTEGQKSGFLRISNLQKQDQ  FDF03
61   LAIVPNVRISWRRGHFHGQSFYSTRPPSIHKDYVNRLFLNWTEGQESGFLRISNLRKEDQ  FDF03-S1
       ++ +                                              +          + +

121  SVYFCRVELDTRSSGRQQWQSIEGTKLSITQAVTTTTQRPSSMTTTWRLSSTTTTTGLRV  FDF03
121  SVYFCRVELDTRRSGRQQLQSIKGTKLTITQAVTTTT........TWRPSSTTTIAGLRV  FDF03-S1
                  +      +    +     +           ++++++++    +      ++

181  TQGKRRSDSWHISLETAVGVAVAVTVLGIMILGLICLL..RWRRRKGQQRTKATTPAREP  FDF03
173  TESKGHSESWHLSLDTAIRVALAVAVLKTVILGLLCLLLLWWRRRKGSRAPSSDF       FDF03-S1
      ++ ++ +    +  +  ++  +  +  +++     +    +++       ++++++++

239  FQNTEEPYENIRNEGQNTDPKLNPKDDGIVYASLALSSSTSPRAPPSHRPLKSPQNETLY  FDF03

299  SVLKA                                                          FDF03
```

+ : residue different or gap

Distribution studies (RT-PCR) shows strong expression in B cells (pool resting + activated), T cells and PBL. Lower expression was observed in monocytes, dendritic cells and granulocytes.

FDF03-M14

The fourth clone, desginated FDF03-M14, is a potential soluble form of human FDF03 generated by alternative splicing. The nucleic acid sequence encoding FDF03-M14 is shown in SEQ ID NO: 7. The amino acid sequence of the FDF03-M-14 protein is shown in SEQ ID NO: 8. cDNA of this molecule was amplified along with that of FDF03 during the analysis of human FDF03 expression by RT-PCR. Using primers designed in the 5'-UTR and 3'-UTR of FDF03 gene (FDF03-U25: 5'-ACAGCCC-TCTTCGGAGCCTCA (SEQ ID NO: 11) and FDF03-L1166: 5'-AGCTGGCCCTGA-ACTCCTGG (SEQ ID NO: 12)), an approximately 200 base pair shorter band was amplified by RT-PCR from activated PBL cDNA, then gel purified, cloned and sequenced. One clone (M14) contained an insert of 908 base pairs with an ORF encoding a type I protein of 175 amino acids. cDNA alignments with FDF03 sequence identified a deletion of 253 nucleotides in FDF03-M14 sequence (FDF03 nucleotide 608 to 861) that deleted the sequences encoding the extracellular threonine-rich region, the transmembrane domain and the start of the intracytoplasmic domain of FDF03, and that introduced a prematured stop codon at position 655 of FDF03-M14. The deduced amino acid sequence of FDF03-M14 resulted in a protein with a potential hydrophobic signal peptide followed by an extracellular Ig like-domain that matched perfectly with that of FDF03, but that was linked to a COOH-terminal 24 amino acid sequence different from FDF03. This molecule may be the product of an alternative splicing of FDF03 mRNA.

Like FDF03-ΔTM, this molecule may represent a secreted soluble form of FDF03 and may bind to the same ligand(s) as FDF03. The amino acid sequence is shown below, wherein the signal sequence is underlined.

MGRPLLLPLLPLLLPPAFLQPSGSTGSGPSYLYGVTQPKHLSASMGGSVEIPFSFYYPWEL
ATAPDVRISWRRGHFHGQSFYSTRPPSIHKDYVNRLFLNWTEGQKSGFLRISNLQKQDQSV
YFCRVELDTRSSGRQQWQSIEGTKLSITQGNPSKTQRSHMRISGMRDKIQIPS (SEQ ID
NO: 8)

The protein alignment of FDF03 (SEQ ID NO: 2) and FDF03-M14 (SEQ ID NO: 8) is shown below.

```
1    MGRPLLLPLLPLLLPPAFLQPSGSTGSGPSYLYGVTQPKHLSASMGGSVEIPFSFYYPWE    FDF03
1    MGRPLLLPLLPLLLPPAFLQPSGSTGSGPSYLYGVTQPKHLSASMGGSVEIPFSFYYPWE    FDF03-14

61   LATAPDVRISWRRGHFHGQSFYSTRPPSIHKDYVNRLFLNWTEGQKSGFLRISNLQKQDQ    FDF03
61   LATAPDVRISWRRGHFHGQSFYSTRPPSIHKDYVNRLFLNWTEGQKSGFLRISNLQKQDQ    FDF03-M14
```

```
121  SVYFCRVELDTRSSGRQQWQSIEGTKLSITQAVTTTTQRPSSMTTTWRLSSTTTTTGLRV     FDF03
121  SVYFCRVELDTRSSGRQQWQSIEGTKLSITQGNPSKTQRSHMRISGMRDKIQIPS          FDF03-M14
                               *****   ******** *******

181  TQGKRRSDSWHISLETAVGVAVAVTVLGIMILGLICLLRWRRRKGQQRTKATTPAREPFQ     FDF03

241  NTEEPYENIRNEGQNTDPKLNPKDDGIVYASLALSSSTSPRAPPSHRPLKSPQNETLYSVLKA  FDF03

*: residue different
```

FDF03-S2

The fifth clone, designated FDF03-S2 is an Ig-like molecule homologous to FDF03 but with a short intracytoplasmic domain and a charged residue in transmembrane domain. This molecule is highly homologous to FDF03-S1 and is a potential DAP12-associated protein. The nucleic acid sequence encoding FDF03-S2 is shown is SEQ ID NO: 9. The amino acid sequence of the FDF03-S2 protein is shown in SEQ ID NO: 10.

cDNA of this molecule was amplified using primers specific for FDF03-S2. Specificity is obtained with forward primer designed in 5'UTR of FDF03-S2. FDF03-S2-forward: 5'-CAAGG- GATAAAAAGGCAC (SEQ ID NO: 13) (does not amplify FDF03, FDF03ΔTM or FDF03-S1). FDF03-S2-reverse: 5'-AACTCTCCTCCAGTCGGT (SEQ ID NO: 14) (can amplify FDF03-S1, but not FDF03 or FDF03deltaTM).

FDF03-S2 is a type I transmembrane protein belonging to the Ig superfamily. FDF03-S2 contains a hydrophobic leader sequence followed by an extracellular region (~170 residues) with one V-type Ig domain structure homologous to that of FDF03 (~85% homology at the amino acid level). Unlike FDF03, FDF03-S2 possesses a transmembrane domain with a charged amino acid (K), and a small intracellular tail (15 residues) without ITIM or internalization motif. FDF03-S2 is highly homologous to FDF03-S1 (3 amino acid difference in the extracellular domain and one amino acid missing in the transmembrane domain). Like FDF03-S1, FDF03-S2 may represent an activation isoform of FDF03 and may associate with ITAM-bearing molecules such as DAP12.

There are two putative start codons in frame (position 117 and 309). The first one is not contained within a typical Kozak sequence. The sequence shown below is deduced from the second start codon (nucleotide 309), as starting at the first start codon in frame (position 117) does not encode for a hydrophobic sequence followed by another Ig-like domain. In the sequence shown below, the signal peptide and transmembrane domain are underlined. The charged amino acid, lysine (K) residue (arrow) in transmembrane domain may permit association with another chain, for example DAP12.

MGRPLLLPLLLLLLQPPAFLQPGGSTGSGPSYLYGVTQPKHLSASMGGSVEIPFSFYYPWE
LATAPDVRISWRRGHFHGQSFYSTRPPSIHKDYVNRLFLNWTEGQESGFLRISNLRKEDQ
SVYFCRVELDTRRSGRQQLQSIKGTKLTITQAVTTTTTWRPSSTTTIAGLRVTESKGHSE
SWHLSLDTAIRVALAVAVLKTVILGLLCLLLWWRRRKGSRAPSSDF
↑

The protein alignments of FDF03, FDF03-S1 and FDF03-S2 is shown below.

```
1    MGRPLLLPLLPLLLPPAFLQPSGSTGSGPSYLYGVTQPKHLSASMGGSVEIPFSFYYPWE  FDF03
1    MGRPLLLPLLLLLQPPAFLQPGGSTGSGPSYLYGVTQPKHLSASMGGSVEIPFSFYYPWE  FDF03-S1
1    MGRPLLLPLLLLLQPPAFLQPGGSTGSGPSYLYGVTQPKHLSASMGGSVEIPFSFYYPWE  FDF03-S2
               +  +        +

61   LATAPDVRISWRRGHFHGQSFYSTRPPSIHKDYVNRLFLNWTEGQKSGFLRISNLQKQDQ  FDF03
61   LAIVPNVRISWRRGHFHGQSFYSTRPPSIHKDYVNRLFLNWTEGQESGFLRISNLRKEDQ  FDF03-S1
61   LATAPDVRISWRRGHFHGQSFYSTRPPSIHKDYVNRLFLNWTEGQESGFLRISNLRKEDQ  FDF03-S2
** *                                          +         + +

121  SVYFCRVELDTRSSGRQQWQSIEGTKLSITQAVTTTTQRPSSMTTTWRLSSTTTTTGLRV  FDF03
121  SVYFCRVELDTRRSGRQQLQSIKGTKLTITQAVTTTT........TWRPSSTTTIAGLRV  FDF03-S1
121  SVYFCRVELDTRRSGRQQLQSIKGTKLTITQAVTTTT........TWRPSSTTTIAGLRV  FDF03-S2
                +     +   +    +          ++++++++   +     ++

181  TQGKRRSDSWHISLETAVGVAVAVTVLGIMILGLICLL..RWRRRKGQQRTKATTPAREP  FDF03
173  TESKGHSESWHLSLDTAIRVALAVAVLKTVILGLLCLLLLWWRRRKGSRAPSSDF       FDF03-S1
173  TESKGHSESWHLSLDTAIRVALAVAVLKTVILGLLCLLL.WWRRRKGSRAPSSDF       FDF03-S2
      ++ ++ +   +  +  ++  +  +  +++    +   +*+      ++++++++

239  FQNTEEPYENIRNEGQNTDPKLNPKDDGIVYASLALSSSTSPRAPPSHRPLKSPQNETLY  FDF03

299  SVLKA                                                          FDF03
```

+ : residue different or gap between FDF03-S2/FDF03-S1 and FDF03
* : residue different or gap between FDF03-S2/FDF03 and FDF03-S1

Distribution studies (RT-PCR) shows expression in activated dendritic cells (CD34-derived), PBMC, monocytes and tonsil B cells.

Alignment with human IgV domains and TCR V domain is given below. This alignment shows the conserved VDJ structure of FDF03.

```
Ig V region QVQ.LQESGPG.LVKPSETLSLTCTVSGGSVSSGSYYWSW.IRQAPGKGLEWIG
TCR human   QVQ.LQESGPG.LVKPSETLSLTCTVSGYSISSG.YYWGW.IRQPPGKGLEWIG
FDF03       QPSGSTGSGPSYLYGVTQPKHLSASMGGSVEIPFSFYYPWELATAPDVRISWRR
FDF03-S1     QPGGSTGSGPSYLYGVTQPKHLSASMGGSVEIPFSFYYPWELAIVPNVRISWRR
FDF03-S2     QPGGSTGSGPSYLYGVTQPKHLSASMGGSVEIPFSFYYPWELATAPDVRISWRR
            +      +++  +         +     +         + +     +     +

Ig V region YIYYSGSTNY.......NRSHKSRVNIS.VDTAKNQFSLKLSSVSTADTAVYYCARIT
TCR human   SIYHSGSTYY.......NPSLKSRVTIS.VDTSKNQFSLKLSSVTAADTAVYYCARVR
FDF03       GHFH.GQSFYSTRPPSIHKDYVNRLFLNWTEGQKSGF.LRISNLQKQDQSVYFC.RVE
FDF03-S1     GHFH.GQSFYSTRPPSIHKDYVNRLFLNWTEGQESGF.LRISNLRKEDQSVYFC.RVE
FDF03-S2     GHFH.GQSFYSTRPPSIHKDYVNRLFLNWTEGQESGF.LRISNLRKEDQSVYFC.RVE
                 +   +             +             + +  +     +  ++ + +


Ig V region TTVPSSWYYYYMDVWDKGTTVTVSS
TCR human   RRYSSSAS...KIIFGSGTRLSIR.
FDF03       LDTRSSGRQQWQS..IEGTKLSITQ
FDF03-S1     LDTRRSGRQQLQS..IKGTKLTITQ
FDF03-S2     LDTRRSGRQQLQS..IKGTKLTITQ
                 +          ++
```

Studies of human genomic DNA clones show that chromosome 7 contains both FDF03-S1 and FDF03 specific sequences, confirming that the two molecules are encoded by two different genes. These studies also suggest that FDF03-S1 and -S2 genes are two different alleles of the same gene. In addition, PCR from intronic sequence surrounding the areas of difference between S1 and S2 on genomic DNA from different donors shows the existence of homozygotes and S1/S2 heterozygotes at this locus. It is thus likely that these two cDNAs are from different alleles.

The genomic organization of the FDF03 gene confirms that FDF03-ΔTM is produced by alternative splicing (deletion of exon 3 coding for the hinge region and TM domain). This is also the case for FDF03-M14 (deletion of exons 3 and 4).

The two forms of FDF03-S1/2 may be advantageously used as population markers. The two forms of this protein will either not bind the same ligand (e.g., as in the case of the NK receptor family) or will bind at different affinities, thus potentially giving individuals a different response to receptor/ligand interaction.

The localization of the genes encoding FDF03 (including the ΔTM and M14 forms) and FDF03-S1 on human chromosome 7q22 is interesting because this region is frequently deleted in myelodystrophic syndromes such as Acute Myeloid Leukemia (AML). The implication of the possible deletion of a myeloid inhibitory receptor in a proliferative disease leads to a possibile use in gene therapy.

Nucleic Acids, Vectors, and Host Cells

The invention provides nucleic acid sequences, in particular the nucleic acid sequences shown in SEQ ID NO: 1, 5, 7 or 9 or nucleic acid sequences which encode an amino acid sequences shown in SEQ ID NO: 2, 4, 6, 8 or 10. The invention encompasses isolated nucleic acid fragments comprising all or part of the individual nucleic acid sequences disclosed herein. The nucleic acid sequences of the invention comprise at least about 12, preferably at least about 18, more preferably at least about 20-35 and most preferably at least about 35-55 or more consecutive nucleotides, including complete protein-coding sequences, or complements thereof. The invention encompasses sequence-conservative variants and function-conservative variants of these sequences.

Nucleic acids comprising any of the sequences disclosed herein or subsequences thereof can be prepared by standard methods using the nucleic acid sequence information provided in SEQ ID NO: 1, 3, 5, 7 and 9. For example, nucleic acids can be chemically synthesized using, e.g., the phosphoramidite solid support method of Matteucci *et al.*,

1981, *J. Am. Chem. Soc.* **103**:3185, the method of Yoo *et al.*, 1989, *J. Biol. Chem.* **764**:17078, or other well known methods. This can be done by sequentially linking a series of oligonucleotide cassettes comprising pairs of synthetic oligonucleotides. The nucleic acids may be isolated directly from cells. Alternatively, the polymerase chain reaction (PCR) method can be used to produce the nucleic acids of the invention, using either chemically synthesized strands or genomic material as templates. Primers used for PCR can be synthesized using the sequence information provided herein and can further be designed to introduce appropriate new restriction sites, if desirable, to facilitate incorporation into a given vector for recombinant expression. Of course, due to the degeneracy of the genetic code, many different nucleotide sequences can encode polypeptides having the amino acid sequences defined by SEQ ID NO: 2, 4, 6, 8 or 10 subsequences thereof. The codons can be selected for optimal expression in prokaryotic or eukaryotic systems. Such degenerate variants are also encompassed by this invention.

The encoded polypeptides may be expressed by using many known vectors such as pUC plasmids, pET plasmids (Novagen, Inc., Madison, WI), or pRSET or pREP (Invitrogen, San Diego, CA), and many appropriate host cells such as *Escherichia coli*, *Saccharomyces cerevisiae*, and insect and mammalian cell lines using methods known to those skilled in the art. The particular choice of vector/host is not critical to the practice of the invention.

The nucleic acids of the present invention find use, e.g., as templates for the recombinant production of peptides or polypeptides, as probes and primers for the detection of the human genes described herein, for chromosome mapping, and as probes or to design PCR primers to identify homologous genes in other mammalian species. Homology may be determined experimentally. Alternatively, homology analysis may be performed computationally. In practicing the present invention, a gene that shares at least about 70% DNA sequence homology at the nucleotide level with the genome of another mammalian species is considered to be present in that species. The determination that a gene is present in another mammal may be achieved using any technique known in the art. Appropriate techniques include without limitation hybridization to genomic DNA, colony hybridization to a genomic or cDNA library, polymerase chain reaction (PCR) using degenerate primers or gene-specific primers and genomic DNA as a template, genetic complementation, antibody cross-reactivity, or biochemical complementation *in vitro*.

In applying these techniques, conditions are established that discriminate different levels of homology between probe and template. For example, for hybridization of a

probe to immobilized DNA (whether in a Southern blot, dot blot, or colony hybridization format), varying the SSC concentration in the buffer allows the detection of hybrids having different levels of homology (1X SSC is 0.15 M NaCl - 0.015 M Na citrate). In a wash buffer containing 6M urea and 0.4% sodium dodecyl sulfate, the presence of 2X SSC, 0.5X SSC, 0.1X SSC, and 0.05X SSC allows the formation of hybrids having threshold homologies of at least 55% + 5%, 65% + 5%, 75% + 5%, and >85%, respectively. Preferably, once a gene has been identified in another organism by hybridization or PCR, the DNA sequence of the gene is determined directly.

It will be understood that some methods that detect homologous sequences may result in the identification or isolation of only a portion of the entire protein-coding sequence of a particular gene. The entire protein-coding sequence can be isolated and identified, for example, by using an isolated nucleic acid encoding the known portion of the sequence, or fragments thereof, to prime a sequencing reaction with cDNA as template; this is followed by sequencing the amplified product. The isolated nucleic acid encoding the disclosed sequence, or fragments thereof, can also be hybridized to appropriate cDNA libraries to identify clones containing additional complete segments of the protein-coding sequence of which the shorter sequence forms a part. Then, the entire protein-coding sequence, or fragments thereof, or nucleic acids encoding all or part of the sequence, or sequence-conservative or function-conservative variants thereof, may be employed in practicing the present invention.

In a similar manner, additional sequences derived from the 5' and 3' flanking regions of sequence encoding the protein, including regulatory sequences, may be isolated, and the nucleotide sequence determined.

Polypeptides

Both the naturally occurring and recombinant forms of the polypeptides described herein, including both glycosylated and non-glycosylated forms are encompassed by the invention. The polypeptides of the present invention, including function-conservative variants, may be isolated from human monocytes, or from heterologous organisms or cells (e.g., bacteria, fungi, insect, plant, and mammalian cells) into which a protein-coding sequence has been introduced and expressed. The proteins described herein, or portions thereof, also may be expressed as fusions with other proteins. The polypeptides may be chemically synthesized by commercially available automated procedures, including, without limitation, exclusive solid phase synthesis, partial solid phase

methods, fragment condensation or classical solution synthesis. The polypeptides can also, advantageously, be made by *in vitro* translation.

Methods for polypeptide purification are well-known in the art, including, without limitation, preparative disc-gel electrophoresis, isoelectric focusing, sucrose density gradient centrifugation, HPLC, reversed-phase HPLC, gel filtration, ion exchange and partition chromatography, and countercurrent distribution. For some purposes, it is preferable to produce the polypeptide in a recombinant system in which the protein contains an additional sequence tag that facilitates purification, such as, but not limited to, a polyhistidine sequence. The polypeptide can then be purified from a crude lysate of the host cell by chromatography on an appropriate solid-phase matrix. Alternatively, antibodies produced against a protein or against peptides derived therefrom can be used as purification reagents. Other purification methods are possible.

The present invention also encompasses derivatives and homologues of the polypeptides specifically disclosed herein. For some purposes, nucleic acid sequences encoding the peptides may be altered by substitutions, additions, or deletions that provide for functionally equivalent molecules, i.e., function-conservative variants. For example, one or more amino acid residues within the sequence can be substituted by another amino acid of similar properties, such as, for example, positively charged amino acids (arginine, lysine, and histidine); negatively charged amino acids (aspartate and glutamate); polar neutral amino acids; and non-polar amino acids.

The isolated polypeptides may be modified by, for example, phosphorylation, sulfation, acylation, or other protein modifications. They may also be modified with a label capable of providing a detectable signal, either directly or indirectly, including, but not limited to, radioisotopes and fluorescent compounds.

The polypeptides of the invention find use, e.g., for binding studies, for construction and expression of modified molecules, for structure/function studies and for the preparation of polyclonal and monoclonal antibodies. Polypeptides useful as immunogenic components for preparing antibodies or as targets for binding agent studies are at least five or more residues in length. Preferably, the polypeptides comprise at least about 12, more preferably at least about 20, and most preferably at least about 30 or more residues. Methods for obtaining these polypeptides are well known and are explained in *Immunochemical Methods in Cell and Molecular Biology*, 1987 (Mayer and Waler, eds; Academic Press, London); Scopes, 1987, *Protein Purification: Principles and Practice*, Second Edition (Springer-Verlag, N.Y.) and *Handbook of Experimental Immunology*, 1986, Volumes I-IV (Weir and Blackwell, eds.).

Having isolated one member of a binding partner of a specific interaction, methods exist for isolating the counter-partner. See, e.g., Gearing *et al.*, 1989, *EMBO J.* **8**:3667-3676. Many methods of screening for binding activity are known by those skilled in the art and may be used to practice the invention. For example, an expression library can be screened for specific binding to the protein, e.g., by cell sorting, or other screening to detect subpopulations which express such a binding component. See, e.g., Ho *et al.*, 1993, *Proc. Natl. Acad. Sci. USA* **90**:11267-11271. Alternatively, a panning method may be used. See, e.g., Seed and Aruffo, 1987, *Proc. Natl. Acad. Sci. USA* **84**:3365-3369. A two-hybrid selection system may also be applied making appropriate constructs with the available protein sequences. See, e.g., Fields and Song, 1989, *Nature* **340**:245-246. Several methods of automated assays have been developed in recent years so as to permit screening of tens of thousands of compounds in a short period of time.

Physical Variants

This invention also encompasses proteins or peptides having substantial amino acid sequence similarity with an amino acid sequence of a SEQ ID NO: 2, 4, 6, 8 or 10. Variants exhibiting substitutions, e.g., 20 or fewer, preferably 10 or fewer, and more preferably 5 or fewer substitutions, are encompassed. Where the substitutions are conservative substitutions, the variants will share immunogenic or antigenic similarity or cross-reactivity with a corresponding natural sequence protein. Natural variants include individual, allelic, polymorphic, strain, or species variants.

Amino acid sequence similarity, or sequence identity, is determined by optimizing residue matches, if necessary, by introducing gaps as required. This changes when considering conservative substitutions as matches. Conservative substitutions typically include substitutions within the following groups: glycine, alanine; valine, isoleucine, leucine; aspartic acid, glutamic acid; asparagine, glutamine; serine, threonine; lysine, arginine; and phenylalanine, tyrosine. Homologous amino acid sequences include natural allelic and interspecies variations in each respective protein sequence. Typical homologous proteins or peptides will have from 50-100% similarity (if gaps can be introduced), to 75-100% similarity (if conservative substitutions are included) with the amino acid sequence of the relevant protein. Identity measures will be at least about 50%, generally at least 60%, more generally at least 65%, usually at least 70%, more usually at least 75%, preferably at least 80%, and more preferably at least 80%, and in particularly preferred embodiments, at least 85% or more. See also Needleham *et al.*, 1970, *J. Mol. Biol.* 48:443-453; Sankoff *et al.*, 1983, *Time Warps, String Edits, and*

Macromolecules: The Theory and Practice of Sequence Comparison Chapter One, Addison-Wesley, Reading, MA; and software packages from IntelliGenetics, Mountain View, CA; and the University of Wisconsin Genetics Computer Group (GCG), Madison, WI.

Nucleic acids encoding the corresponding proteins will typically hybridize to SEQ ID NO: 1, 3, 5, 7 or 9 under stringent conditions. For example, nucleic acids encoding the respective proteins will typically hybridize to the nucleic acid of SEQ ID NO: 1, 3, 5, 7 or 9 under stringent hybridization conditions, while providing few false positive hybridization signals. Generally, stringent conditions are selected to be about 10° C lower than the thermal melting point (Tm) for the sequence being hybridized to at a defined ionic strength and pH. The Tm is the temperature (under defined ionic strength and pH) at which 50% of the target sequence hybridizes to a perfectly matched probe. Typically, stringent conditions will be those in which the salt concentration in wash is about 0.02 molar at pH 7 and the temperature is at least about 50° C. Other factors may significantly affect the stringency of hybridization, including, among others, base composition and size of the complementary strands, the presence of organic solvents such as formamide, and the extent of base mismatching. A preferred embodiment will include nucleic acids that will bind to disclosed sequences in 50% formamide and 20-50 mM NaCl at 42° C.

An isolated nucleic acid can be readily modified by nucleotide substitutions, nucleotide deletions, nucleotide insertions, and inversions of nucleotide stretches. These modifications result in novel DNA sequences which encode these antigens, their derivatives, or proteins having highly similar physiological, immunogenic, or antigenic activity.

Modified sequences can be used to produce mutant antigens or to enhance expression. Enhanced expression may involve gene amplification, increased transcription, increased translation, and other mechanisms. Such mutant protein derivatives include predetermined or site-specific mutations of the respective protein or its fragments. "Mutant protein" encompasses a polypeptide otherwise falling within the homology definition of the proteins as set forth above, but having an amino acid sequence which differs from that of the protein as found in nature, whether by way of deletion, substitution, or insertion. In particular, "site specific mutant protein" generally includes proteins having significant similarity with a protein having a sequence of SEQ ID NO: 2, 4, 6, 8 or 10. Generally, the variant will share many physicochemical and biological

activities, e.g., antigenic or immunogenic, with those sequences, and in preferred embodiments contain most or all of the disclosed sequence.

Glycosylation alterations are included, e.g., made by modifying the glycosylation patterns of a polypeptide during its synthesis and processing, or in further processing steps. Particularly preferred means for accomplishing this are by exposing the polypeptide to glycosylating enzymes derived from cells that normally provide such processing, e.g., mammalian glycosylation enzymes. Deglycosylation enzymes are also contemplated. Also embraced are versions of the same primary amino acid sequence which have other minor modifications, including phosphorylated amino acid residues, e.g., phosphotyrosine, phosphoserine, or phosphothreonine, or other moieties, including ribosyl groups or cross-linking reagents. Also, proteins comprising substitutions are encompassed, which should retain substantial immunogenicity, to produce antibodies that recognize a protein of SEQ ID NO: 2, 4, 6, 8 or 10. Typically, these proteins will contain less than 20 residue substitutions from the disclosed sequence, more typically less than 10 substitutions, preferably less than 5, and more preferably less than three. Alternatively, proteins that begin and end at structural domains will usually retain antigenicity and cross immunogenicity.

A major group of derivatives are covalent conjugates of the proteins described herein or fragments thereof with other proteins or polypeptides. These derivatives can be synthesized in recombinant culture such as N- or C-terminal fusions or by the use of agents known in the art for their usefulness in cross-linking proteins through reactive side groups. Preferred protein derivatization sites with cross-linking agents are at free amino groups, carbohydrate moieties, and cysteine residues.

Fusion polypeptides between these proteins and other homologous or heterologous proteins are also provided. Heterologous polypeptides may be fusions between different surface markers, resulting in, e.g., a hybrid protein. Likewise, heterologous fusions may be constructed which would exhibit a combination of properties or activities of the derivative proteins. Typical examples are fusions of a reporter polypeptide, e.g., luciferase, with a segment or domain of a protein, e.g., a receptor-binding segment, so that the presence or location of the fused protein may be easily determined. See, e.g., U.S. Patent No. 4,859,609. Other gene fusion partners include bacterial ß-galactosidase, trpE, Protein A, ß-lactamase, alpha amylase, alcohol dehydrogenase, and yeast alpha mating factor. See, e.g., Godowski *et al.*, 1988, *Science* **241**:812-816.

Such polypeptides may also have amino acid residues that have been chemically modified by phosphorylation, sulfonation, biotinylation, or the addition or removal of other moieties, particularly those that have molecular shapes similar to phosphate groups. In some embodiments, the modifications will be useful labeling reagents, or serve as purification targets, e.g., affinity ligands.

This invention also contemplates the use of derivatives of these proteins other than variations in amino acid sequence or glycosylation. Such derivatives may involve covalent or aggregative association with chemical moieties. These derivatives generally fall into the three classes: (1) salts, (2) side chain and terminal residue covalent modifications, and (3) adsorption complexes, for example with cell membranes. Such covalent or aggregative derivatives are useful as immunogens, as reagents in immunoassays, or in purification methods such as for affinity purification of ligands or other binding ligands. For example, a protein antigen can be immobilized by covalent bonding to a solid support such as cyanogen bromide-activated Sepharose, by methods which are well known in the art, or adsorbed onto polyolefin surfaces, with or without glutaraldehyde cross-linking, for use in the assay or purification of antibodies. The proteins can also be labeled with a detectable group, e.g., radioiodinated by the chloramine T procedure, covalently bound to rare earth chelates, or conjugated to another fluorescent moiety for use in diagnostic assays. Purification of these proteins may be accomplished by immobilized antibodies.

Antibodies

The immunogenic components of this invention, as discribed above, are useful as antigens for preparing antibodies by standard methods. Such immunogenic components can be produced by proteolytic cleavage of larger polypeptides or by chemical synthesis or recombinant technology and are thus not limited by proteolytic cleavage sites. Preferably, smaller immunogenic components will first be rendered more immunogenic by cross-linking or by coupling to an immunogenic carrier molecule (i.e., a macromolecule having the property of independently eliciting an immunological response in a host animal, to which the immunogenic components of the invention can be covalently linked). Cross-linking or conjugation to a carrier molecule may be required because small polypeptide fragments sometimes act as haptens (molecules which are capable of specifically binding to an antibody but incapable of eliciting antibody production, i.e., they are not immunogenic). Conjugation of such fragments to an

immunogenic carrier molecule renders them immunogenic through what is commonly known as the "carrier effect".

Antibodies according to the present invention include polyclonal and monoclonal antibodies. The antibodies may be elicited in an animal host by immunization with immunogenic components of the invention or may be formed by *in vitro* immunization (sensitization) of immune cells. The immunogenic components used to elicit the production of antibodies may be isolated from human cells (e.g., human monocytes) or chemically synthesized. The antibodies may also be produced in recombinant systems programmed with appropriate antibody-encoding DNA. Alternatively, the antibodies may be constructed by biochemical reconstitution of purified heavy and light chains.

The antibodies of this invention can be purified by standard methods, including but not limited to preparative disc-gel electrophoresis, isoelectric focusing, HPLC, reversed-phase HPLC, gel filtration, ion exchange and partition chromatography, and countercurrent distribution. Purification methods for antibodies are disclosed, e.g., in *The Art of Antibody Purification*, 1989, Amicon Division, W.R. Grace & Co. General protein purification methods are described in *Protein Purification: Principles and Practice*, R.K. Scopes, Ed., 1987, Springer-Verlag, New York, NY.

Suitable adjuvants for the vaccination of animals include but are not limited to Adjuvant 65 (containing peanut oil, mannide monooleate and aluminum monostearate); Freund's complete or incomplete adjuvant; mineral gels such as aluminum hydroxide, aluminum phosphate and alum; surfactants such as hexadecylamine, octadecylamine, lysolecithin, dimethyldioctadecyl-ammonium bromide, N,N-dioctadecyl-N',N'-bis(2-hydroxymethyl) propane-diamine, methoxyhexadecylglycerol and pluronic polyols; polyanions such as pyran, dextran sulfate, poly IC, polyacrylic acid and carbopol; peptides such as muramyl dipeptide, dimethylglycine and tuftsin; and oil emulsions. The immunogenic components could also be administered following incorporation into liposomes or other microcarriers. Information concerning adjuvants and various aspects of immunoassays are disclosed, e.g., in the series by P. Tijssen, 1987, *Practice and Theory of Enzyme Immunoassays*, 3rd Edition, Elsevier, New York.

Serum produced from animals thus immunized can be used directly. Alternatively, the IgG fraction can be separated from the serum using standard methods such as plasmaphoresis or adsorption chromatography using IgG specific adsorbents such as immobilized Protein A.

Hybridomas of the invention used to make monoclonal antibodies against the immunogenic components of the invention are produced by well-known techniques.

Usually, the process involves the fusion of an immortalizing cell line with a B-lymphocyte that produces the desired antibody. Alternatively, non-fusion techniques for generating immortal antibody-producing cell lines are possible, and come within the purview of the present invention, e.g., virally-induced transformation, Casali *et al.*, 1986, *Science* **234**:476. Immortalizing cell lines are usually transformed mammalian cells, particularly myeloma cells of rodent, bovine, and human origin. Most frequently, rat or mouse myeloma cell lines are employed as a matter of convenience and availability.

Techniques for obtaining the appropriate lymphocytes from mammals injected with the immunogenic components are well known. Generally, peripheral blood lymphocytes (PBLs) are used if cells of human origin are desired, or spleen cells or lymph node cells are used if non-human mammalian sources are desired. A host animal is injected with repeated dosages of a preferably purified immunogenic component, and the animal is permitted to generate the desired antibody-producing cells before these are harvested for fusion with the immortalizing cell line. Techniques for fusion are also well known in the art, and in general involve mixing the cells with a fusing agent, such as polyethylene glycol.

Hybridomas are selected by standard procedures, such as HAT (hypoxanthine-aminopterin-thymidine) selection. From among these hybridomas, those secreting the desired antibody are selected by assaying their culture medium by standard immunoassays, such as Western blotting, ELISA (enzyme-linked immunosorbent assay), RIA (radioimmunoassay), or the like. Antibodies are recovered from the medium using standard protein purification techniques. Tijssen, 1985, *Practice and Theory of Enzyme Immunoassays*, Elsevier, Amsterdam.

Many references are available for guidance in applying any of the above techniques: Kohler *et al.*, 1980, *Hybridoma Techniques*, Cold Spring Harbor Laboratory, New York; Tijssen, 1985, *Practice and Theory of Enzyme Immunoassays*, Elsevier, Amsterdam; Campbell, 1984, *Monoclonal Antibody Technology*, Elsevier, Amsterdam; Hurrell, 1982, *Monoclonal Hybridoma Antibodies: Techniques and Applications*, CRC Press, Boca Raton, FL. Monoclonal antibodies can also be produced using well known phage library systems.

The use and generation of antibody fragments is also well known, e.g., Fab fragments: Tijssen, 1985, *Practice and Theory of Enzyme Immunoassays*, Elsevier, Amsterdam; Fv fragments: Hochman *et al.*, 1973, *Biochemistry* **12**:1130; Sharon *et al.*, 1976, *Biochemistry* **15**:1591; Ehrlich *et al.*, U.S. Patent No. 4,355,023; and antibody half

molecules: Auditore-Hargreaves, U.S. Patent No. 4,470,925. These also may be useful in immunoassays.

These antibodies, whether polyclonal or monoclonal, can be used, e.g., in an immobilized form bound to a solid support by well known methods, to isolate and purify the immunogenic components by immunoaffinity chromatography. The antibodies are useful as probes to distinguish tissue and cell type distribution. The antibodies may be used to screen expression libraries for particular expression products. Usually the antibodies used in such a procedure will be labeled with a moiety allowing easy detection of presence of antigen by antibody binding. Antibodies to proteins may be used for the analysis or, or identification of specific cell population components which express the respective protein. By assaying the expression products of cells expressing the proteins described herein it is possible to diagnose disease, e.g., immune-compromised conditions, monocyte depleted conditions, or overproduction of monocytes. Antibodies raised against the proteins will also be useful to raise anti-idiotypic antibodies. These will be useful in detecting or diagnosing various immunological conditions related to expression of the respective antigens. The present invention encompasses antibodies that specifically recognize monocyte-derived immunogenic components. Such antibodies can be used conventionally, e.g., as reagents for purification of monocyte cell components, or in diagnostic applications.

Diagnostic Applications

The invention encompasses compositions, methods, and kits useful in clinical settings for the qualitative or quantitative diagnosis, i.e., detection of specific components in a biological sample. These applications utilize nucleic acids, peptides/polypeptides, or antibodies specific for the components described herein. Both antibody-based and nucleic acid-based diagnostic methods, including PCR-based diagnostic methods are contemplated. Detection of the level of monocyte cells present in a sample is important for diagnosis of certain aberrant disease conditions. For example, an increase in the number of monocytes in a tissue or the lymph system can be indicative of the presence of a monocyte hyperplasia, tissue or graft rejection, or inflammation. A low monocyte population can indicate an abnormal reaction to, e.g., a bacterial or viral infection, which may require an appropriate treatment to normalize the monocyte response.

Both the naturally occurring and the recombinant form of the proteins of this invention are particularly useful in kits and assay methods which are capable of screening compounds for binding activity to the proteins

In nucleic-acid-type diagnostic methods, the sample to be analyzed may be contacted directed with the nucleic acid probes. Probes include oligonucleotides at least 12 nucleotides, preferably at least 18, and most preferably 20-35 or more nucleotides in length. Alternatively, the sample may be treated to extract the nucleic acids contained therein. It will be understood that the particular method used to extract DNA will depend on the nature of the biological sample. The resulting nucleic acid from the sample may be subjected to gel electrophoresis or other size separation techniques, or, the nucleic acid sample may be immobilized on an appropriate solid matrix without size separation or used for PCR.

Kits suitable for antibody-based diagnostic applications typically include one or more of the following components:

(i) Antibodies: The antibodies may be pre-labeled; alternatively, the antibody may be unlabelled and the ingredients for labeling may be included in the kit in separate containers, or a secondary, labeled antibody is provided; and

(ii) Reaction components: The kit may also contain other suitably packaged reagents and materials needed for the particular immunoassay protocol, including solid-phase matrices, if applicable, and standards.

Kits suitable for nucleic acid-based diagnostic applications typically include the following components:

(i) *Probe DNA*: The probe DNA may be pre-labeled; alternatively, the probe DNA may be unlabelled and the ingredients for labeling may be included in the kit in separate containers; and

(ii) *Hybridization reagents*: The kit may also contain other suitably packaged reagents and materials needed for the particular hybridization protocol, including solid-phase matrices, if applicable, and standards.

PCR based diagnostic kits are also contemplated and are encompassed by the invention.

The kits referred to above may include instructions for conducting the test. Furthermore, in preferred embodiments, the diagnostic kits are adaptable to high-throughput and/or automated operation.

Therapeutic Applications

The invention also provides reagents that may exhibit significant therapeutic value. The proteins (naturally occurring or recombinant), fragments thereof, and antibodies thereto, along with compounds identified as having binding affinity to the

proteins, may be useful in the treatment of conditions associated with abnormal physiology or development. For example, a disease or disorder associated with abnormal expression or abnormal signaling by a monocyte, e.g., as an antigen presenting cell, is a target for an agonist or antagonist of the protein. The proteins likely play a role in regulation or development of hematopoietic cells, e.g., lymphoid cells, which affect immunological responses, e.g., antigen presentation and the resulting effector functions.

Other abnormal developmental conditions are known in cell types shown to possess monocyte protein mRNA by northern blot analysis. See Berkow (ed.) The Merck Manual of Diagnosis and Therapy, Merck & Co., Rahway, NJ; and Thorn, et al. Harrison's Principles of Internal Medicine, McGraw-Hill, NY. Developmental or functional abnormalities, e.g., of the immune system, cause significant medical abnormalities and conditions that may be susceptible to prevention or treatment using compositions provided herein.

Recombinant monocyte-derived proteins or antibodies of the invention may be purified and then administered to a patient. These reagents can be combined for therapeutic use with additional active or inert ingredients, e.g., in conventional pharmaceutically acceptable carriers or diluents, e.g., immunogenic adjuvants, along with physiologically innocuous stabilizers and excipients. In particular, these may be useful in a vaccine context, where the antigen is combined with one of these therapeutic versions of agonists or antagonists. These combinations can be sterile filtered and placed into dosage forms as by lyophilization in dosage vials or storage in stabilized aqueous preparations. This invention also contemplates use of antibodies or binding fragments thereof, including forms which are not complement binding.

Drug screening using antibodies or receptor or fragments thereof can identify compounds having binding affinity to these monocyte-derived proteins, including isolation of associated components. Subsequent biological assays can then be utilized to determine if the compound blocks or antagonizes the activity of the protein. Likewise, a compound having intrinsic stimulating activity might activate the cell through the protein and is thus an agonist. This invention further contemplates the therapeutic use of antibodies to the proteins as antagonists.

The quantities of reagents necessary for effective therapy will depend upon many different factors, including means of administration, target site, physiological state of the patient, and other medicants administered. Thus, treatment dosages should be titrated to optimize safety and efficacy. Typically, dosages used in vitro may provide useful guidance in the amounts useful for in situ administration of these reagents. Animal

testing of effective doses for treatment of particular disorders will provide further predictive indication of human dosage. Various considerations are described, e.g., in Gilman, et al. (eds.) (1990) Goodman and Gilman's: The Pharmacological Bases of Therapeutics (8th ed.) Pergamon Press; and (1990) Remington's Pharmaceutical Sciences (17th ed.) Mack Publishing Co., Easton, PA. Methods for administration are discussed therein and below, e.g., for oral, intravenous, intraperitoneal, or intramuscular administration, transdermal diffusion, and others. Pharmaceutically acceptable carriers will include water, saline, buffers, and other compounds described, e.g., in the Merck Index, Merck & Co., Rahway, NJ. Dosage ranges would ordinarily be expected to be in amounts lower than 1 mM concentrations, typically less than about 10 μM concentrations, usually less than about 100 nM, preferably less than about 10 pM (picomolar), and most preferably less than about 1 fM (femtomolar), with an appropriate carrier. Slow release formulations, or a slow release apparatus will often be utilized for continuous administration.

The proteins, antagonists, and agonists could be administered directly to the host to be treated or, depending on the size of the compounds, it may be desirable to conjugate them to carrier proteins such as ovalbumin or serum albumin prior to their administration. Therapeutic formulations may be administered in many conventional dosage formulations. While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical formulation. Formulations typically comprise at least one active ingredient, as defined above, together with one or more acceptable carriers thereof. Each carrier should be both pharmaceutically and physiologically acceptable in the sense of being compatible with the other ingredients and not injurious to the patient. Formulations include those suitable for oral, rectal, nasal, or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. See, e.g., Gilman, et al. (eds.) (1990) Goodman and Gilman's: The Pharmacological Bases of Therapeutics (8th ed.) Pergamon Press; and (1990) Remington's Pharmaceutical Sciences (17th ed.) Mack Publishing Co., Easton, PA; Avis, et al. (eds.) (1993) Pharmaceutical Dosage Forms: Parenteral Medications Dekker, NY; Lieberman, et al. (eds.) (1990) Pharmaceutical Dosgae Forms: Tablets Dekker, NY; and Lieberman, et al. (eds.) (1990) Pharmaceutical Dosage Forms: Disperse Systems Dekker, NY. The therapy of this invention may be combined with or used in association with other chemotherapeutic or chemopreventive agents.

Many modifications and variations of this invention can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. The specific embodiments described herein are offered by way of example only, and the invention is to be limited only by the terms of the appended claims, along with the full scope of equivalents to which such claims are entitled.

WHAT IS CLAIMED IS:

1. An isolated polypeptide comprising an amino acid sequence derived from SEQ ID NO: 2, 4, 6, 8 or 10.

2. The polypeptide of claim 1 comprising the amino acid sequence of the mature protein.

3. An isolated nucleic acid comprising a nucleotide sequence encoding an amino acid sequence derived from SEQ ID NO: 2, 4, 6, 8 or 10.

4. The nucleic acid of claim 3 wherein the nucleotide sequence encodes the mature protein.

5. The nucleic acid of claim 4 comprising the nucleotide sequence shown in SEQ ID: NO 1, 3, 5, 7 or 9.

6. A fusion protein comprising the polypeptide of claim 1.

7. A binding compound which specifically binds to the polypeptide of claim 1.

8. The binding compound of claim 7 which is an antibody or antibody fragment.

9. The binding compound of claim 8 wherein the anitbody is a monoclonal antibody.

10. An expression vector comprising the nucleic acid of claim 3.

11. A host cell comprising the vector of claim 10.

12. A process for recombinatly producing a polypeptide comprising culturing the host cell of claim 11 under conditions in which the polypeptide is expressed.

13. A method for detecting a specific nucleic acid sequence in a sample, said method comprising the steps of:

(i) contacting a sample suspected to contain a specific nucleic acid sequence with a probe comprising a nucleic acid sequence comprising at least 8 consecutive nucleotides

selected from SEQ ID NO: 1, 3, 5, 7, or 9 under conditions in which a hybrid can form between said probe and the specific nucleic acid in said sample; and

(ii) detecting any hybrid formed in step (i),

wherein detection of said hybrid indicates the presence of the specific nucleic acid sequence in said sample.

14. The method of claim 13 further comprising amplifying said specific sequence in said sample prior to said detecting step.

15. A method for detecting a specific antigenic component in a sample, said method comprising the steps of:

(i) contacting a sample suspected to contain a specific antigenic component encoded by an amino acid sequence derived from SEQ ID NO: 2, 4, 6, 8, or 10 with an antibody specific for said component, under conditions in which a stable antigen-antibody complex can form between said antibody and said antigenic component in said sample; and

(ii) detecting any antigen-antibody complex formed in step (i),

wherein detection of an antigen-antibody complex indicates the presence of said antigenic component in said sample.

16. A method of screening for candidate therapeutic agents comprising:

selecting as a target sequence a polypeptide having an amino acid sequence derived from SEQ ID NO: 2, 4, 6, 8 or 10;

contacting a test compound with said target sequence; and

selecting as candidate therapeutic agent those test compounds which bind to the target sequence.

SEQUENCE LISTING

<110> Bates, Elizabeth
Fournier, Nathalie
Chalus, Lionel
Garrone, Pierre

<120> MONOCYTE-DERIVED NUCLEIC ACIDS AND RELATED COMPOSITIONS AND METHODS

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Ala Thr Ala Pro Asp Val Arg Ile Ser Trp Arg Arg Gly His Phe His
 45                  50                  55                  60

ggg cag tcc ttc tac agc aca agg ccg cct tcc att cac aag gat tat        408
Gly Gln Ser Phe Tyr Ser Thr Arg Pro Pro Ser Ile His Lys Asp Tyr
                 65                  70                  75

gtg aac cgg ctc ttt ctg aac tgg aca gag ggt cag aag agc ggc ttc        456
Val Asn Arg Leu Phe Leu Asn Trp Thr Glu Gly Gln Lys Ser Gly Phe
             80                  85                  90

ctc agg atc tcc aac ctg cag aag cag gac cag tct gtg tat ttc tgc        504
Leu Arg Ile Ser Asn Leu Gln Lys Gln Asp Gln Ser Val Tyr Phe Cys
         95                  100                 105

cga gtt gag ctg gac aca cgg agc tca ggg agg cag cag tgg cag tcc        552
Arg Val Glu Leu Asp Thr Arg Ser Ser Gly Arg Gln Gln Trp Gln Ser
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atc gag ggg acc aaa ctc tcc atc acc cag ggt cag cag cgg act aaa        600
Ile Glu Gly Thr Lys Leu Ser Ile Thr Gln Gly Gln Gln Arg Thr Lys
125                 130                 135                 140

gcc aca acc cca gcc agg gaa ccc ttc caa aac aca gag gag cca tat        648
Ala Thr Thr Pro Ala Arg Glu Pro Phe Gln Asn Thr Glu Glu Pro Tyr
                145                 150                 155

gag aat atc agg aat gaa gga caa aat aca gat ccc aag cta aat ccc        696
Glu Asn Ile Arg Asn Glu Gly Gln Asn Thr Asp Pro Lys Leu Asn Pro
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aag gat gac ggc atc gtc tat gct tcc ctt gcc ctc tcc agc tcc acc        744
Lys Asp Asp Gly Ile Val Tyr Ala Ser Leu Ala Leu Ser Ser Ser Thr
        175                 180                 185

tca ccc aga gca cct ccc agc cac cgt ccc ctc aag agc ccc cag aac        792
Ser Pro Arg Ala Pro Pro Ser His Arg Pro Leu Lys Ser Pro Gln Asn
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Glu Thr Leu Tyr Ser Val Leu Lys Ala
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Pro Asp Val Arg Ile Ser Trp Arg Arg Gly His Phe His Gly Gln Ser
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Phe Tyr Ser Thr Arg Pro Pro Ser Ile His Lys Asp Tyr Val Asn Arg
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 80                  85                  90                  95

Ser Asn Leu Gln Lys Gln Asp Gln Ser Val Tyr Phe Cys Arg Val Glu
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Leu Asp Thr Arg Ser Ser Gly Arg Gln Gln Trp Gln Ser Ile Glu Gly
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Thr Lys Leu Ser Ile Thr Gln Gly Gln Gln Arg Thr Lys Ala Thr Thr
    130                 135                 140

Pro Ala Arg Glu Pro Phe Gln Asn Thr Glu Glu Pro Tyr Glu Asn Ile
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Arg Asn Glu Gly Gln Asn Thr Asp Pro Lys Leu Asn Pro Lys Asp Asp
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Gly Ile Val Tyr Ala Ser Leu Ala Leu Ser Ser Ser Thr Ser Pro Arg
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cagacatctg tgcctcattc ctgatctcaa ggggaaagca agaacaaggg aggcttcctc      180

aggatctcga acctgcggaa ggaggaccag tctgtgtact tctgccaagt ccagctggac      240

atacagatca gggaggctgt cgtggcagtc catcaagggg acccacctca ccatcaccca      300

ggccctcagg cagcccctcc acagggcccc tctcctgcct ggacagctct gctggtctcc      360

ccgtcccctg gagaagaaca aggcc atg ggt cgg ccc ctg ctg ctg ccc ctg        412
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Leu Leu Leu Leu Gln Pro Pro Ala Phe Leu Gln Pro Gly Gly Ser Thr
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gga tct ggt cca agc tac ctt tat ggg gtc act caa cca aaa cac ctc        508
Gly Ser Gly Pro Ser Tyr Leu Tyr Gly Val Thr Gln Pro Lys His Leu
     10                  15                  20

tca gcc tcc atg ggt ggc tct gtg gaa atc ccc ttc tcc ttc tat tac        556
Ser Ala Ser Met Gly Gly Ser Val Glu Ile Pro Phe Ser Phe Tyr Tyr
 25                  30                  35                  40

ccc tgg gag tta gcc ata gtt ccc aac gtg aga ata tcc tgg aga cgg        604
Pro Trp Glu Leu Ala Ile Val Pro Asn Val Arg Ile Ser Trp Arg Arg
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ggc cac ttc cac ggg cag tcc ttc tac agc aca agg ccg cct tcc att        652
Gly His Phe His Gly Gln Ser Phe Tyr Ser Thr Arg Pro Pro Ser Ile
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cac aag gat tat gtg aac cgg ctc ttt ctg aac tgg aca gag ggt cag        700
His Lys Asp Tyr Val Asn Arg Leu Phe Leu Asn Trp Thr Glu Gly Gln
         75                  80                  85

gag agc ggc ttc ctc agg atc tca aac ctg cgg aag gag gac cag tct        748
Glu Ser Gly Phe Leu Arg Ile Ser Asn Leu Arg Lys Glu Asp Gln Ser
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gtg tat ttc tgc cga gtc gag ctg gac acc cgg aga tca ggg agg cag        796
Val Tyr Phe Cys Arg Val Glu Leu Asp Thr Arg Arg Ser Gly Arg Gln
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cag ttg cag tcc atc aag ggg acc aaa ctc acc atc acc cag gct gtc        844
Gln Leu Gln Ser Ile Lys Gly Thr Lys Leu Thr Ile Thr Gln Ala Val
                125                 130                 135

aca acc acc acc acc tgg agg ccc agc agc aca acc acc ata gcc ggc        892
Thr Thr Thr Thr Thr Trp Arg Pro Ser Ser Thr Thr Thr Ile Ala Gly
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Leu Arg Val Thr Glu Ser Lys Gly His Ser Glu Ser Trp His Leu Ser
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ctg gac act gcc atc agg gtt gca ttg gct gtc gct gtg ctc aaa act        988
Leu Asp Thr Ala Ile Arg Val Ala Leu Ala Val Ala Val Leu Lys Thr
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185                 190                 195                 200

aaa ggt agc agg gcg cca agc agt gac ttc tgaccaacag agtgtgggga      1086
Lys Gly Ser Arg Ala Pro Ser Ser Asp Phe
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ctcgttcccc attggcaaga tacatggaga gcaccctgag gacctttaaa aggcaaagcc  1206

gcaaggcaga aggaggctgg gtccctgaat caccgactgg aggagagtta cctacaagag  1266

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ttaaaccact ggcatttggg ggctgtttat tatagcagtg caaagagttc ctttatcctc  1386

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                  20                  25                  30

Val Glu Ile Pro Phe Ser Phe Tyr Tyr Pro Trp Glu Leu Ala Ile Val
              35                  40                  45

Pro Asn Val Arg Ile Ser Trp Arg Arg Gly His Phe His Gly Gln Ser
          50                  55                  60

Phe Tyr Ser Thr Arg Pro Pro Ser Ile His Lys Asp Tyr Val Asn Arg
      65                  70                  75

Leu Phe Leu Asn Trp Thr Glu Gly Gln Glu Ser Gly Phe Leu Arg Ile
 80                  85                  90                  95

Ser Asn Leu Arg Lys Glu Asp Gln Ser Val Tyr Phe Cys Arg Val Glu
                100                 105                 110

Leu Asp Thr Arg Arg Ser Gly Arg Gln Gln Leu Gln Ser Ile Lys Gly
            115                 120                 125

Thr Lys Leu Thr Ile Thr Gln Ala Val Thr Thr Thr Thr Thr Trp Arg
        130                 135                 140

Pro Ser Ser Thr Thr Thr Ile Ala Gly Leu Arg Val Thr Glu Ser Lys
    145                 150                 155
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Gly His Ser Glu Ser Trp His Leu Ser Leu Asp Thr Ala Ile Arg Val
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Ala Leu Ala Val Ala Val Leu Lys Thr Val Ile Leu Gly Leu Leu Cys
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aacaaggcc atg ggt cgg ccc ctg ctg ctg ccc cta ctg ccc ctg ctg ctg 171
          Met Gly Arg Pro Leu Leu Leu Pro Leu Leu Pro Leu Leu Leu
                  -15                 -10                 -5

ccg cca gca ttt ctg cag cct agt ggc tcc aca gga tct ggt cca agc   219
Pro Pro Ala Phe Leu Gln Pro Ser Gly Ser Thr Gly Ser Gly Pro Ser
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tac ctt tat ggg gtc act caa cca aaa cac ctc tca gcc tcc atg ggt   267
Tyr Leu Tyr Gly Val Thr Gln Pro Lys His Leu Ser Ala Ser Met Gly
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ggc tct gtg gaa atc ccc ttc tcc ttc tat tac ccc tgg gag tta gcc   315
Gly Ser Val Glu Ile Pro Phe Ser Phe Tyr Tyr Pro Trp Glu Leu Ala
 30                  35                  40                  45

aca gct ccc gac gtg aga ata tcc tgg aga cgg ggc cac ttc cac ggg   363
Thr Ala Pro Asp Val Arg Ile Ser Trp Arg Arg Gly His Phe His Gly
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cag tcc ttc tac agc aca agg ccg cct tcc att cac aag gat tat gtg   411
Gln Ser Phe Tyr Ser Thr Arg Pro Pro Ser Ile His Lys Asp Tyr Val
             65                  70                  75

aac cgg ctc ttt ctg aac tgg aca gag ggt cag aag agc ggc ttc ctc   459
Asn Arg Leu Phe Leu Asn Trp Thr Glu Gly Gln Lys Ser Gly Phe Leu
         80                  85                  90
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gtt gag ctg gac aca cgg agc tca ggg agg cag cag tgg cag tcc atc 555
Val Glu Leu Asp Thr Arg Ser Ser Gly Arg Gln Gln Trp Gln Ser Ile
110 115 120 125

gag ggg acc aaa ctc tcc atc acc cag ggg aac cct tcc aaa aca cag 603
Glu Gly Thr Lys Leu Ser Ile Thr Gln Gly Asn Pro Ser Lys Thr Gln
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agg agc cat atg aga ata tca gga atg aag gac aaa ata cag atc cca 651
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Ser

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Thr Ala Pro Asp Val Arg Ile Ser Trp Arg Arg Gly His Phe His Gly
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Gln Ser Phe Tyr Ser Thr Arg Pro Pro Ser Ile His Lys Asp Tyr Val
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Arg Ile Ser Asn Leu Gln Lys Gln Asp Gln Ser Val Tyr Phe Cys Arg
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Val Glu Leu Asp Thr Arg Ser Ser Gly Arg Gln Gln Trp Gln Ser Ile
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Glu Gly Thr Lys Leu Ser Ile Thr Gln Gly Asn Pro Ser Lys Thr Gln
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cagccctctg gggagcctca ccctggctct ccccactcac ctcagccctc aggcagcccc 240

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acaaggcc atg ggt cgg ccc ctg ctg ctg ccc ctg ctg ctc ctg ctg cag  350
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Pro Pro Ala Phe Leu Gln Pro Gly Gly Ser Thr Gly Ser Gly Pro Ser
         -1   1                5                  10

tac ctt tat ggg gtc act caa cca aaa cac ctc tca gcc tcc atg ggt   446
Tyr Leu Tyr Gly Val Thr Gln Pro Lys His Leu Ser Ala Ser Met Gly
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ggc tct gtg gaa atc ccc ttc tcc ttc tat tac ccc tgg gag tta gcc   494
Gly Ser Val Glu Ile Pro Phe Ser Phe Tyr Tyr Pro Trp Glu Leu Ala
 30                  35                  40                  45

aca gct ccc gac gtg aga ata tcc tgg aga cgg ggc cac ttc cac ggg   542
Thr Ala Pro Asp Val Arg Ile Ser Trp Arg Arg Gly His Phe His Gly
                 50                  55                  60

cag tcc ttc tac agc aca agg ccg cct tcc att cac aag gat tat gtg   590
Gln Ser Phe Tyr Ser Thr Arg Pro Pro Ser Ile His Lys Asp Tyr Val
             65                  70                  75

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aag ggg acc aaa ctc acc atc acc cag gct gtc aca acc acc acc acc   782
Lys Gly Thr Lys Leu Thr Ile Thr Gln Ala Val Thr Thr Thr Thr Thr
                130                 135                 140

tgg agg ccc agc agc aca acc acc ata gcc ggc ctc agg gtc aca gaa   830
Trp Arg Pro Ser Ser Thr Thr Thr Ile Ala Gly Leu Arg Val Thr Glu
            145                 150                 155

agc aaa ggg cac tca gaa tca tgg cac cta agt ctg gac act gcc atc   878
Ser Lys Gly His Ser Glu Ser Trp His Leu Ser Leu Asp Thr Ala Ile
        160                 165                 170

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ctg tgc ctc ctc ctg tgg tgg agg aga agg aaa ggt agc agg gcg cca   974
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            65                  70                  75

Asn Arg Leu Phe Leu Asn Trp Thr Glu Gly Gln Glu Ser Gly Phe Leu
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Arg Ile Ser Asn Leu Arg Lys Glu Asp Gln Ser Val Tyr Phe Cys Arg
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Val Glu Leu Asp Thr Arg Arg Ser Gly Arg Gln Gln Leu Gln Ser Ile
110                 115                 120                 125

Lys Gly Thr Lys Leu Thr Ile Thr Gln Ala Val Thr Thr Thr Thr Thr
                130                 135                 140

Trp Arg Pro Ser Ser Thr Thr Thr Ile Ala Gly Leu Arg Val Thr Glu
            145                 150                 155

Ser Lys Gly His Ser Glu Ser Trp His Leu Ser Leu Asp Thr Ala Ile
        160                 165                 170

Arg Val Ala Leu Ala Val Ala Val Leu Lys Thr Val Ile Leu Gly Leu
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INTERNATIONAL SEARCH REPORT

Int. .tional Application No
PCT/US 99/30004

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/12 C12N15/62 C07K14/705 C07K16/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 24906 A (SCHERING CORP) 11 June 1998 (1998-06-11) cited in the application SEQ ID NOs:1 and 2. page 36, line 1 - line 4 page 37, line 19 - line 28	1-16
X	WO 98 25959 A (CHIRON CORP) 18 June 1998 (1998-06-18) SEQ ID NOs:2 and 21 page 20, line 28 -page 21, line 19	1-16
X	WO 98 44113 A (GENETICS INST) 8 October 1998 (1998-10-08) SEQ ID NOs:7 and 8 page 40, line 18 -page 41, line 17 claim 19	1-16

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 June 2000	26/06/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Mata Vicente, T.

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INTERNATIONAL SEARCH REPORT

Int. ational Application No
PCT/US 99/30004

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document. with indication.where appropriate. of the relevant passages	Relevant to claim No.
P,X	WO 99 18243 A (MILLENNIUM BIOTHERAPEUTICS INC) 15 April 1999 (1999-04-15) SEQ ID NOs:1 and 2. abstract -----	1-16

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/30004

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9824906 A	11-06-1998	AU 5587298 A	29-06-1998
		EP 0948623 A	13-10-1999
WO 9825959 A	18-06-1998	AU 5796298 A	03-07-1998
		EP 0948531 A	13-10-1999
WO 9844113 A	08-10-1998	AU 6590898 A	22-10-1998
		EP 0970209 A	12-01-2000
WO 9918243 A	15-04-1999	AU 9790798 A	27-04-1999